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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/578,693	05/26/2000	Masaya Yamanouchi	20-4710P	9841

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/578,693	YAMANOUCHI ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *3/20/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4,6,9,16-19,21-24 and 27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4,6,9,16-19,21-24 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment Entry

1. Applicant's response to the Office Action mailed September 20, 2005 is acknowledged (paper filed 3/20/06). Claims 2, 4, 6, 9, 16, 17, 18, 19, 21, 22, and 24 have been modified. Claims 1, 3, 5, 7, 8, 10-15, 20, and 25-26 have been canceled. New claim 27 has been added. Currently claims 2, 4, 6, 9, 16-19, 21-24 and 27 are currently pending and under examination.

NEW GROUNDS OF REJECTIONS NECESSITATED BY AMENDMENT

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 2, 4, 6, 16, 17, 18, 22, 23, 24, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorski et al. (Clinical Chemistry, 43, No.1, January 1997, pages 193-195) in view of Maatman et al. (Biochem. J. 1992, 288, pages 285-290) and Simon et al. (The Journal of Biological Chemistry, 272(16) 4/18/97, 10652-10663).

Gorski et al. disclose a comparative study evaluating the increased concentration of fatty acid binding protein (FABP) concentrations in plasma samples of patients with chronic renal failure. Plasma FABP concentration was measured by a sensitive noncompetitive sandwich ELISA. PAGE 194 2nd column. Urine measurements of increased FABP are taught on page 193, 3rd column.

Plasma FABP concentration is shown to markedly increase in patients with chronic renal failure. Page 194, 3rd column. The findings suggest that the kidney plays a dominant role in the clearance of plasma FABP. Page 194 3rd column.

Gorski et al. differ from the instant invention in not specifically teaching the detection of liver-type fatty acid binding protein.

However, Maatman et al. identified the liver-type fatty acid binding protein utilized in the instant invention. Page 285, 1st column. This is supported by Applicants arguments (page 24 of the response filed 9/14/01 in paper #7). Maatmann et al. discloses liver-type fatty acid binding proteins and speculates that it is utilized in nephrotoxicity. Maatman et al. teaches that L-FABP and H-FABP were found in the kidney (found in kidney tissue). See page 289.

While, Simon et al. teach that the liver fatty acid binding protein functions to suppress expression in the proximal nephron (kidney tissue). See abstract and page 10655.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the liver-type fatty acid binding protein as taught by Maatmann et al., having proven function is the kidney (nephron) as taught by Simon et al. to detect the specific kidney diseases relating to FABP in the method of Gorski et al. because both Maatman and Simon taught that L-FABP was located in the kidney and Maatman et al. taught that "the liver-type FABP binds various ligands and may be involved in the renal excretion of exogenous and endogenous metabolites. The liver-type FABP also binds some drugs and may in this way prevent nephrotxicity". Page 289, 2nd column 1st paragraph. While, Simon et al. demonstrated that the liver fatty acid binding protein [heptad repeat] mediate suppression in the stomach, liver, and kidney and represents a target for identifying transcription factors that regulate gene expression. See page 10662-1st column-last paragraph.

II. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gorski et al. (Clinical Chemistry, 43, No.1, January 1997, pages 193-195) in view of Maatman et al. (Biochem. J. 1992, 288, pages 285-290) and Simon et al.(The Journal of Biological Chemistry, 272(16) 4/18/97, 10652-10663) and further in view of Kimura et al. (Journal of Biological Chemistry, 3/25/91, Vol.266., No.9., pages 5963-5972).

See discussion of Gorski et al. in view of Maatman et al. and Simon et al. as set forth above.

Gorski et al. in view of Maatman et al. and Simon et al. differ from the instant invention in failing to teach that the liver-type FABP is found in the proximal tubule of the kidney and does not cross-react with a heart muscle-type fatty acid binding protein.

However, these characteristics of α_{2U}–globulin were already known in the prior art. Specifically Kimura et al. disclose that fatty acid-binding proteins found in the kidney could be distinguished according to their primary structure and histologic distribution. Two specific FABPs weighing 14 and 15.5 kDa were found in male rat kidney cytosol. The 14 kDa compound was identified as heart FABP and localized in the cytoplasm of the epithelia of the kidney distal tubules. The 15.5 kDa compound was identified as a proteolytically modified form of α_{2U}–globulin (alpha 2u-globulin) and localized in the endosomes or lysosomes of kidney proximal tubules.

Gorski et al. in view of Maatman et al. and Simon et al. and in further view of Kimura et al. are all analogous art because they are from the same field of endeavor, both inventions teach methods involving FABP detection.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antibody which would not cross-react with a muscle-type fatty acid binding protein as taught by Kimura et al., to detect the specific kidney FABP in the method of Gorski et al. in view of Maatman et al. and Simon et al. because such antibodies as taught by Kimura et al. are well known in the art.

A person of ordinary skill in the art would have had a reasonable expectation of success utilizing such antibody assays, because Kimura et al. had already taught that the kidney contained two different types of fatty acid binding proteins, one designated the heart-FABP and the other designated the kidney-FABP. (page 5964, Results).

One having ordinary skill in the art would have been motivated to distinguish between the two types by employing an antibody that would not cross react with the other type (heart-FABP/kidney distal tubules) in order to receive an accurate, more precise measure of the concentration of the FABP of interest (in this case kidney-FABP/ kidney proximal tubules).

III. Claims 19 and 21 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gorski et al. (Clinical Chemistry, 43, No.1, January 1997, pages 193-195) in view of Maatman et al. (Biochem. J. 1992, 288, pages 285-290) and Simon et al.(The Journal of Biological Chemistry, 272(16) 4/18/97, 10652-10663) and further in view of Galaske et al. (Pflugers Archives European Journal of Physiology, 1978, 375,3, 269-277-ABSTRACT ONLY).

Please see previous discussions of Gorski et al. in view of Maatman et al. and Simon et al.

Gorski et al. in view of Maatman et al. and Simon et al. differ from the instant invention in not teaching a detection system involving a chronic renal disease (anti-GMB-nephritis model) further monitoring specimen collection at various intervals.

Galaske et al. disclosed the glomerular filtration and tubular uptake of plasma proteins in the acute heterologus phase of an anti-GMB nephritis model. Injections of anti-glomerular-basement membrane serum (anti-GMB-serum) were evaluated in tubular reabsorption and tubular flow at various times. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a anti-GMB nephritis model as taught by Galaske et al., to detect kidney diseases via proteins in the method of Gorski et al. in view of Maatman et al. and Simon et al. because Galaske et al. disclose that such models existed allowing for protein detection in plasma and urine.

One of ordinary skill in the art would have been motivated to do this in order to detect renal disorders at the onset and follow the disease progression/regression.

Response to Arguments

3. Applicant's arguments filed March 20, 2005 have been fully considered but they are not persuasive.

Applicants contend that prior art does not disclose or suggest the claimed element of diagnosing or prognosing kidney disease and the assertion that L-FABP and H-FABP as equivalent compounds is improper. In response to these arguments, it is noted that the prior art teaches FABP measurement to kidney diseases such as chronic renal failure.

See for example, Gorski et al. page 194, 3rd column; on page 289, 2nd column of Maatmann et al. liver-type fatty acid binding proteins are suggested for use in renal excretion and nephrotoxicity, while Simon et al. teach that the liver fatty acid binding protein functions to suppress expression in the proximal nephron (kidney). See abstract and page 10655.

The instant specification identifies nephritis and chronic renal failure as kidney diseases. For example, see page 1 lines 16-25. Accordingly the prior art teaches the kidney disease identified in the instant disclosure.

With respect to the argument that L-FABP and H-FABP are not equivalent. It is noted that it is examiners position that various FABPs are found and recognized in the prior art. For example see Gorski et al. page 193 3rd column. Gorski et al. measure plasma FABP levels and disclose that its levels increase in chronic renal failure. See Gorski et al. Table 1 on page 194 and page 195 1st column. Gorski et al. are silent about which specific type of FABP is elevated but suggest that the values must be evaluated along with the source, rate of release, and elimination from the plasma. See page 194 1st column. The prior art sited in combination with Gorski et al. further discloses that the liver-type FABP is found in the kidney and involved in kidney functions. Specifically, Maatman et al. taught that "the liver-type FABP binds various ligands and may be involved in the renal excretion of exogenous and endogenous metabolites. The liver-type FABP also binds some drugs and may in this way prevent nephrotxicity". Page 289, 2nd column 1st paragraph. While, Simon et al. demonstrated that the liver fatty acid binding protein [heptad repeat] mediate suppression in the stomach, liver, and kidney and represents a target for identifying transcription factors that regulate gene expression. See page 10662-1st column-last paragraph.

Therefore it would have been obvious to one of ordinary skill in the art to measure L-FABP as an indicator of kidney disease since L-FABP linked to the kidney and Gorski et al. has demonstrated increased FABP levels in chronic renal failure.

Applicant contends that Gorski utilizes FABP as a marker for myocardial infarction. This argument was carefully considered but not found persuasive because it is well-established that consideration of a reference is not limited to the preferred embodiments or working examples, but extends to the entire disclosure for what it fairly teaches, when viewed in light of the admitted knowledge in the prior art. *In re Boe*, 355 F.2d 961, 148 USPQ 507, 510 (CCPA 1966); *In re Lambert*, 545 F.2d 747, 750, 192 USPQ 279, 280 (CCPA 1976). In this instant, Gorski et at were the first to demonstrate increased plasma FABP concentrations in patients with chronic renal failure and normal heart function. See page 194, 3rd column – 2nd paragraph.

Applicant contends that the FABP of Gorski is a heart type FABP (H-FABP) derived from the heart and Gorski does not even mention L-FABP. This argument was carefully considered but not found persuasive because Gorski does not identify the source of the detected FABP. Although, Gorski does not cite L-FABP it has been sited in combination with Maatman et al. and Simon et al. who teach L-FABP. Even if the FABP taught by Gorski is only H-FABP the prior art teaches that two types of FABP exist in the kidney (H-FABP and L-FABP), therein it would have been obvious to detect either H-FABP or L-FABP in kidney diseases. See Maatman et al. Biochem. J, 1991, 273, 759-766.

Applicant argues that Gorski merely shows increased FABP concentrations in blood samples of patients with kidney failure, but does not disclose the diagnosis or prognosis of kidney disease. This argument was carefully considered but not found persuasive because Gorski et al. teach that the plasma FABP concentration of health persons is relatively low (2-6 $\mu g \bullet L^{-1}$). While, patients with renal failure exhibited increased FABP levels ranging from 12.1 $\mu g \bullet L^{-1}$ to 120.9 $\mu g \bullet L^{-1}$. See page 193 3rd column and Table 1 on page 194.

Thus FABP was increased in renal failure and not in normal patients. In other words increased FABP identified renal failure (diagnosis – identification of a disease or condition).

Applicant argues that Gorski discusses renal failure merely in relation with the diagnosis of myocardial infarction. This argument has been carefully considered but not found persuasive because the instant claims are directed to methods comprising the assessment of kidney disease and does not exclude additional assessments, such as myocardial infarction. Gorski et al. further teaches not only myocardial infarction but is also concerned with chronic renal failure. This is supported on page 194, 1st paragraph "we studied plasma FABP and myoglobin in patients with chronic renal failure" and page 194 3rd paragraph "The present data are the first to show plasma FABP concentration is markedly increased in patients with chronic renal failure and normal heart function, similar to that found for myoglobin."

Applicant argues that Maatman et al. merely speculate that L-FABP may prevent nephrotoxicity, however the function of L-FABP does not shed light on the normal or abnormal levels of FABP in a human specimen. This argument was carefully considered but not found persuasive because Maatman et al. was cited in combination with Gorski et al. Maatman et al. disclose the relevance of L-FABP in the liver (function) and teach the similarities between L-FABP and H-FABP. Gorski et al. teach FABP levels in normal and abnormal human specimens having renal disease. See Gorski et al. page 194, 1st and 3rd columns.

Applicant argues that Simon et al. do not make any connection between an increased in L-FABP protein and kidney disease. This argument was carefully considered but not found persuasive because Simon et al. was merely cited to further support a function of L-FABP in the kidney. See abstract and page 10655.

Where, Simon et al. teach that the liver fatty acid binding protein functions to suppress expression in the proximal nephron (kidney). Simon et al. are cited in combination with in combination with Gorski et al. Gorski et al. teach increased levels of FABP levels renal disease (kidney). See Gorski et al. page 194, 1st and 3rd columns. While, Maatman et al. disclose the relevance of L-FABP in the liver (function) and teach the similarities between L-FABP and H-FABP. While a deficiency in a reference may overcome a rejection under 35 USC 103, a reference is not overcome by pointing out that a reference lacks a teaching for which other references are relied. In re Lyons, 364 F2d 1005, 150 USPQ 741, 746 (CCPA 1966).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988)and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

In this case, Applicant contends that Gorski et al. teach methods of measuring plasma levels of FABP in kidney/renal diseases. While, Maatman et al. and Simon merely speculate as to L-FABPs role in kidney/renal disorders. Therefore there is no motivation to combine Gorski et al., Maatman et al., and Simon et al. This argument was not found persuasive because Maatman et al. disclose that "Based on the RT-PCR and hybridization results, the content of the mRNAs of the liver and heart FABP types do not differ markedly in kidneys of male and female rats". See page 289 1st column and figure 6.

Therefore, one of ordinary skill in the art at the time of applicant's invention would have been motivated to replace the H-FABP of Gorski et al. with the L-FABP taught by Maatman et al. and Simon et al. because the two types of FABP (heart and liver) were both found in the kidney and suggested to have utility in kidney functions.

Also, the test for obviousness is not whether the features of one reference may be bodily incorporated into the other to produce the claimed subject matter but simply what the combination of references makes obvious to one of ordinary skill in the pertinent art. See, *In re Bent*, 52 CCPA 850, 144 USPQ 28, 1964; *In re Nievelt*, 179 USPQ 224 CCPA 1973.

Applicants contend that H-FABP and L-FABP are not the same and are not equivalent. This argument has been carefully considered and found persuasive. This position is withdrawn.

The Declaration under 37 CFR 1.132 filed 3/20/06 of Takeshi Sugaya has been considered but is insufficient to overcome the rejections set forth herein because although H-FABP and L-FABP are structurally different they were both taught by the prior art to be contained within the kidney. FABP increased in renal failure was also demonstrated. Therefore it would have been obvious to one of ordinary skill in the art to measure L-FABP in kidney diseases because it was located in the kidney and taught to play a role in kidney functions.

Attorney's arguments of unexpected results cannot take the place of evidence in the record. In re DeBlauwe, 736 F2d 699, 705, 222 USPQ 191, 196 (Fed Cir 1984). The reference of Gorski et al. taught that plasma FABP concentration is markedly increased in patients with chronic renal failure and normal heart function. See page 194 3rd column 2nd paragraph.

The location of both H-FABP and L-FABP in the kidney is taught by Maatman et al. See page 289 1st and 2nd columns. Thus elevation of H-FABP or L-FABP in renal disease (kidney) is obvious absent evidence to the contrary.

Applicant contends that the reference of Kimura and Galaske do not remedy the deficiencies of Gorski et al., Maatman, and Simon and should therefore be withdrawn. The arguments against Gorski et al., Maatman, and Simon have been addressed above and were not found persuasive. Accordingly the rejections are maintained.

4. For reasons aforementioned, no claims are allowed.

5. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

6. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 – Central Fax number is (571) 273-8300, which is able to receive transmissions 24 hours/day, 7 days/week. In the event Applicant would like to fax an unofficial communication, the Examiner should be contacted for the appropriate Right Fax number.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday - Friday from 7:00 AM - 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see httpr//pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lisa V. Cook
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June 2, 2006

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